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(54) Title: ANALGESIC, ANTI-INFLAMMATORY AND SKELETAL MUSCLE RELAXANT COMPOSITIONS

(57) Abstract

Pharmaceutical compositions and methods of using same comprising at least one non-steroidal anti-inflammatory drug other than aspirin, acetaminophen and phenacetin, in combination with at least one skeletal muscle relaxant, and optionally xanthine or a xanthine derivative, such as caffeine. The xanthine or xanthine derivative has a two-fold benefit; it enhances the effect of the non-steroidal anti-inflammatory drug and its stimulant effect counteracts the sedative effect of the skeletal muscle relaxant.

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ANALGESIC, ANTI-INFLAMMATORY AND SKELETAL MUSCLE RELAXANT COMPOSITIONS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to novel pharmaceutical compositions of matter comprising one or more non-steroidal anti-inflammatory drugs in combination with at least one skeletal muscle relaxant, and optionally a xanthine or xanthine derivative, such as caffeine, and to methods of using said compositions in the treatment of a variety of skeletal muscle disorders including skeletal muscle spasms, certain orthopedic conditions, disk syndromes, low back pain and the like.

Description of the Prior Art

Centrally acting skeletal muscle relaxants are generally prescribed either as single agents or as components of combination products. The Food and Drug Administration has approved indications for these medications as adjuncts to rest and physical therapy for relief of acute, painful musculoskeletal problems. Clinically, the mild pain associated with the majority of cases of minor muscle strains and minor injuries are self limiting. Most patients usually respond rapidly to rest. An anti-inflammatory drug may be useful when there is tissue damage and edema. On the other hand, severe musculoskeletal strains and sprains, trauma, and cervical or lumbar radiculopathy as a consequence of degenerative osteoarthritis, herniated disk, spondylitis or laminectomy, often cause moderate or severe and more chronic painful skeletal muscle spasm. The

principal symptoms include local pain, tenderness on palpation, increased muscle consistency and limitation of motion. For these patients skeletal muscle relaxants alone or in combination with an analgesic are frequently prescribed. Results of some studies have suggested that a formulation of a muscle relaxant and an analgesic provides greater benefit in patients with acute musculoskeletal problems than similar doses of an analgesic alone.

Table I lists several commercial combinations currently available. A current commercial muscle relaxant formulation is Soma® Compound by Carter-Wallace, Inc., which contains 200 mg carisoprodol and 325 mg aspirin. Carisoprodol is a centrally-acting muscle relaxant that does not directly relax tense skeletal muscles in man. Aspirin is a conventional non-narcotic analgesic with anti-inflammatory and antipyretic activity. The most common adverse reactions associated with the use of aspirin in this product have been gastrointestinal, including nausea, vomiting, gastritis, occult bleeding, constipation and diarrhea. Allergic type reactions associated with aspirin may also involve the respiratory tract and skin.

Another commercial skeletal muscle relaxant formulation is Parafon Forte® by McNeil Pharmaceutical. Parafon Forte contains 250 mg chlorzoxazone and 300 mg acetaminophen. Chlorzoxazone is a centrally-acting agent which does not directly relax tense skeletal muscles in man. Acetaminophen, a nonsalicylate analgesic is a conventional non-narcotic analgesic with anti-pyretic activity.

Robaxisal® by A.H. Robins Company, Inc. is another commercial muscle relaxant combination which

contains 400 mg methocarbamol and 325 mg aspirin. The mechanism of action of methocarbamol in humans has not been established, but may be due to general central nervous system depression. Methocarbamol does not directly relax tense skeletal muscles in man. Adverse reactions that have been associated with aspirin in this formulation include: nausea and other gastrointestinal discomfort, gastritis, gastric erosion, vomiting, constipation, diarrhea, angioedema, asthma, rash, pruritis and urticaria.

Norgesic® and Norgesic® Forte are commercial products by Riker Laboratories, Inc. that go one step beyond the previously mentioned products in that Norgesic and Norgesic Forte contain not only a muscle relaxant and aspirin, but they also include caffeine. The specific formulation for Norgesic is 25 mg orphenadrine citrate, 385 mg aspirin and 30 mg caffeine. Norgesic Forte contains 50 mg orphenadrine citrate, 770 mg aspirin and 60 mg caffeine. Orphenadrine citrate is 2-dimethylaminoethyl 2-methylbenzhydryl ether citrate. The common side effects and concerns associated with the use of aspirin occur with the use of Norgesic and Norgesic Forte as well.

TABLE I

Some Combination Products Containing a Skeletal Muscle Relaxant

TRADENAME	CONTENTS OF A SINGLE DOSE				TYPICAL UNIT DOSE PRESENTED AS NO. OF TABLETS
	SKELETAL MUSCLE RELAXANT		ADDITIONAL INGREDIENTS		
SOMA COMPOUND	Carisoprodol	200 mg	aspirin	325 mg	1 - 2
SOMA COMPOUND WITH CODEINE	Carisoprodol	200 mg	aspirin	325 mg	
			codeine PO_4	16 mg	1 - 2
PARAFON FORTE	Chlorzoxazone	250 mg	acetaminophen	300 mg	1 - 2
ROBAXISAL	Methocarbamol	400 mg	aspirin	325 mg	2
NORGESIC	Orphenadrine		aspirin	385 mg	
	Citrate	25 mg	caffeine	30 mg	1 - 2
NORGESIC FORTE	Orphenadrine		aspirin	770 mg	
	Citrate	50 mg	caffeine	60 mg	1/2 - 1

At the present time, one commercial product, Parafon Forte, a skeletal muscle relaxant formulation containing acetaminophen, will be the subject of a hearing granted by the Commissioner of Food and Drugs on a proposal to withdraw approval of its new drug application sometime in 1985. The Director of the Bureau of Drugs of the FDA in a notice published in the Federal Register, 1982, 47 F.R. 22599 concluded that he was unaware of any adequate and well-controlled clinical investigation conducted by experts qualified by scientific training and experience ... [that] demonstrates the effectiveness of Parafon Forte. The present position of the Commissioner of Food and Drugs is set forth below [Federal Register, 1984, 49(200): 48212-48214]:

> Approval of this NDA will be withdrawn unless there exists substantial evidence that Parafon Forte has the clinical effect that it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling....

It should be noted that all of the previously described skeletal muscle relaxant-narcotic analgesic combinations include either aspirin or acetaminophen as the non-narcotic analgesic agent. However, a number of alternative non-narcotic agents offering a variety of advantages over these conventionally employed non-narcotic analgesic antipyretics have now been developed. These newer non-steroidal anti-inflammatory drugs are widely administered orally in the treatment of mild to severe pain, as well as for a variety of disorders including rheumatoid and osteoarthritis.

Within this class of drugs, the compounds vary widely in their chemical structure and in their biological profiles as analgesics, anti-inflammatory agents and antipyretic agents. The principal advantages of these new non-steroidal anti-inflammatory drugs include not only the clinically superior analgesic and anti-inflammatory activity of these agents compared to aspirin, acetaminophen or phenacetin, but also a lessening of the adverse side effects experienced with these conventional agents; more specifically, the gastrointestinal ulcerations and bleeding experienced with aspirin and the hepatic toxicity prevalent with the use of large doses of acetaminophen.

It has further been discovered that by including xanthine or a xanthine derivative, such as caffeine, in these new skeletal muscle relaxant formulations that an especially favorable response can be obtained. The central nervous system stimulant effect of the caffeine is advantageous to counterbalance the sedative effect often resulting from the use of skeletal muscle relaxants. But of even greater significance is the enhanced effect observed by combining a xanthine or a xanthine derivative with a non-steroidal anti-inflammatory drug. An enhanced analgesic or anti-inflammatory response is achieved and lower amounts of the select non-steroidal anti-inflammatory effect are required for the same analgesic or anti-inflammatory effect.

While aspirin and acetaminophen have been utilized in those previous compositions, it has not been heretofore proposed to use any of the newer non-steroidal anti-inflammatory drugs (i.e. excluding aspirin, acetaminophen and phenacetin) in combination with skeletal muscle relaxants and xanthine or a

xanthine derivative, such as caffeine, to achieve more pain relief, a lesser incidence of side effects and thereby a more effective treatment of the musculo-skeletal disorder.

SUMMARY OF THE INVENTION

Surprisingly, the present inventors now find that, the newer non-steroidal anti-inflammatory drugs, which differ substantially in chemical structure from aspirin, acetaminophen and phenacetin, and which have significantly different biological profiles therefrom can be advantageously formulated into a novel composition together with a skeletal muscle relaxant, and optionally xanthine or a xanthine derivative and administered to mammals, especially to humans, to obtain more pain relief and lessened adverse side effects.

It is, therefore, a primary object of the present invention to provide novel pharmaceutical compositions of matter for use in eliciting an analgesic or anti-inflammatory and musculoskeletal relaxing response, said composition comprising an effective analgesic or anti-inflammatory amount of a newer non-steroidal anti-inflammatory drug, an effective amount of a skeletal muscle relaxant, and optionally an amount of xanthine or xanthine derivative, such as caffeine, sufficient to enhance the analgesic or anti-inflammatory effect. Typically, the active ingredients are further associated with a non-toxic pharmaceutically acceptable inert carrier therefrom.

It is a further object of the present invention to provide methods for the treatment of various skeletal muscle disorders in a mammal such as skeletal muscle spasms, certain orthop dic conditions, disk

syndrom s, low back pain and the like, said method comprising administering to said mammal preselected dosages of said non-steroidal anti-inflammatory drug, said skeletal muscle relaxant, and optionally said xanthine or xanthine derivative.

Another object of the present invention is to provide suitable unit dose forms of said composition comprising an effective amount of a non-steroidal anti-inflammatory drug, an effective amount of a skeletal muscle relaxant, and optionally an effective amount of xanthine or a xanthine derivative.

It is a further object of the present invention to administer the novel pharmaceutical compositions containing xanthine or a xanthine derivative, such as caffeine to mammals, especially humans, to not only elicit a more potent analgesic or anti-inflammatory response but also to lessen the sedative effect often resulting from the use of skeletal muscle relaxants.

DETAILED DESCRIPTION OF THE INVENTION

More specifically, the applicants herein have surprisingly found that certain newer non-steroidal anti-inflammatory agents are ideally suited for use in a formulation with skeletal muscle relaxants, and optionally xanthine or a xanthine derivative, such as caffeine, by reason of their enhanced analgesic, anti-inflammatory and antipyretic activity and low incidence of untoward side effects, particularly at the optimum dosages provided for in the present invention, in comparison to aspirin or acetaminophen.

The superiority of various of the non-narcotic analgesics belonging to the newer non-steroidal anti-inflammatory drug class in comparative

studies with aspirin and acetaminophen is well documented in the literature.

Cooper in 1977 found that ibuprofen 400 mg had a greater peak effect and longer duration of action than aspirin 650 mg. Cooper, S.A., Needle, A.E., Kruger, G.O. 1977. "An Analgesic Relative Potency Assay Comparing Aspirin, Ibuprofen and Placebo. "J. Oral Surg. 35:898-903. Cooper in another study in 1982 found 400 mg of ibuprofen to be more effective than aspirin 650 mg. Cooper, S.A., Engel, J., Ladov, M., Precheur, H., Rosenheck, A., Rauch, D. 1982. "Analgesic Efficacy of an Ibuprofen-codeine Combination." Pharmacotherapy 2:162-67. Sunshine et al found ibuprofen to be significantly superior to aspirin in the relief of post-episiotomy pain. Sunshine, A. et al, Clinical Pharmacology and Therapeutics, 24:254-250, 1983.

Dionne in 1982 found ibuprofen to be more effective than acetaminophen in delaying the onset and intensity of post operative dental pain. Dionne, R.A., Campbell, R.A., Cooper, S.A., Hall, D.L., Buckingham, B. "Suppression of Post Operative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen and Acetaminophen Plus Codeine." J. Clin. Pharmacol. (In press).

Naproxen sodium 550 mg was compared with 650 mg of aspirin and was found to provide earlier and better pain relief than aspirin by Seveliüs, H., J. Clin. Pharmacol. 20:480-485, 1980. "Comparative Analgesic Effects of Naproxen Sodium, Aspirin and Placebo."

Both flurbiprofen 50 and 100 mg were significantly more effective than aspirin 600 mg. Flurbiprofen 25 mg was slightly less effective than

aspirin 600 mg. Sunshine, A., Olson N.Z., Laska, E.M. Zighelboim, I., DeCastro, A., Desarrazin, C., Pharmaco Ther. 3:177-181. "Analgesic Effect of Graded Doses of Flurbiprofen in Postepisiotomy Pain".

Silberman found suprofen 200 mg more effective than aspirin 650 mg for pain relief in the treatment of moderate to severe pain resulting from musculoskeletal pain. Silberman, H.M. "Multiple-Dose Comparison of Suprofen, Aspirin and Placebo in the Treatment of Musculoskeletal Pain." Pharmacology 27: S 1, 65-73 (1983).

The outstanding analgesic and anti-inflammatory properties of the non-steroidal anti-inflammatory drugs compared to aspirin or acetaminophen have prompted the widespread acceptance and usage of these newer non-narcotic analgesics, as single entities, for the treatment and management of acute and chronic pain and inflammatory states, notably rheumatoid arthritis and osteoarthritis. However, the utilization of these agents in skeletal muscle relaxant compositions with xanthine or a xanthine derivative has not heretofore been considered.

The non-steroidal anti-inflammatory drugs (NSAID's) for use in the pharmaceutical compositions and methods of use of the present invention may be selected from any of the following categories:

(1) the propionic acid derivatives;

(2) the acetic acid derivatives;

(3) the fenamic acid derivatives;

(4) the biphenylcarboxylic acid derivatives; and

(5) the oxicams.

Accordingly, the term "NSAID" as used herein is intended to mean any non-narcotic analgesic non-

steroidal anti-inflammatory compound, including the pharmaceutically acceptable non-toxic salts thereof, falling within one of the five structural categories above but excluding aspirin, acetaminophen and phenacetin.

The specific compounds falling within the foregoing definition of the non-steroidal anti-inflammatory drugs for use in the present invention are well known to those skilled in the art and reference may be had to various literature reference sources for their chemical structures, pharmacological activities, side effects, normal dosage ranges, etc. See, for example, Physician's Desk Reference, 38th Edition, 1984 and The Merck Index, 9th Edition, Merck and Company, Rahway, New Jersey (1976) and Cutting's Handbook of Pharmacology, 6th Edition, Ed. T. Z. Csaky, M.D., and B.A. Barnes, Appleton-Century-Crofts, New York, 1984, Chapter 49:604-638.

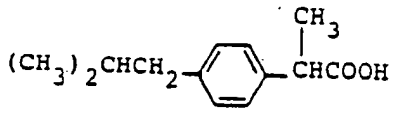
While some of the above-identified compounds are primarily used at the present time as anti-inflammatory agents and others are primarily used as analgesics, in fact all of the contemplated compounds have both analgesic and anti-inflammatory activity and can be used at appropriate dosage levels for either purpose in the compositions and methods of the present invention. The compounds in groups (1) through (4) typically contain a carboxylic acid function; however, those acids are sometimes administered in the form of their pharmaceutically acceptable salts, e.g. sodium salts.

The propionic acid derivatives for use herein include, but are not limited to, ibuprofen, naproxen, naproxen sodium, flurbiprofen, fenoprofen, fenbufen, ketoprofen, pirprofen, carprofen, oxaprozin, prano-

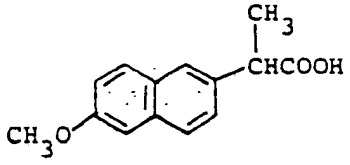
profen, miroprofen, tioxaprofen, suprofen, almino-profen, tiaprofenic acid, fluprofen and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Representative members of the propionic acid group include ibuprofen, naproxen, flurbiprofen, fenbufen, fenoprofen, ibuprofen aluminum, ketoprofen, fluprofen and bucloxic acid. Structural formulas for these representative group members are set forth below:

PROPIONIC ACID DERIVATIVES

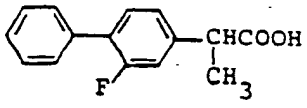
ibuprofen

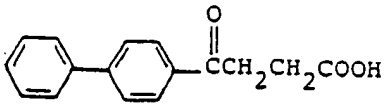


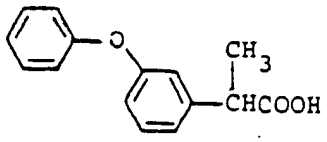
naproxen

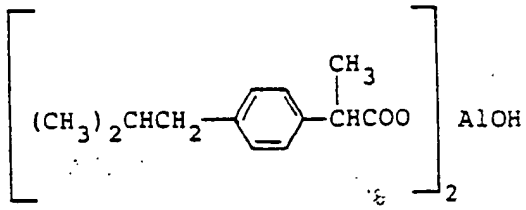


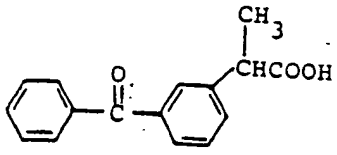
flurbiprofen

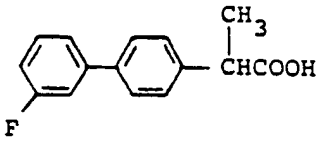


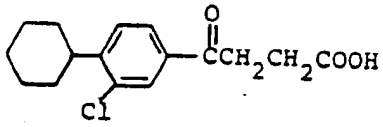
fenbufen 

fenoprofen 

ibuprofen aluminum 

ketoprofen 

fluprofen 

bucloxic acid 

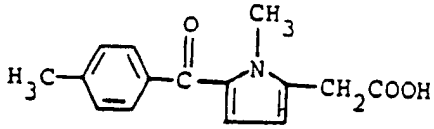
Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH(CH_3)COO^-Na^+$ or $-CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives for use herein include, but are not limited to, indomethacin, sulindac, tolmetin, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxepinac. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this

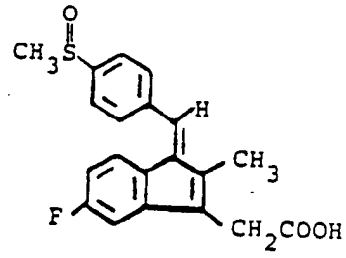
group. Representative members of the acetic acid group include tolmetin, sulindac, indomethacin, diclofenac, alclofenac, fenclozic acid and ibufenac. Structural formulas for these representative group members are set forth below:

ACETIC ACID DERIVATIVES

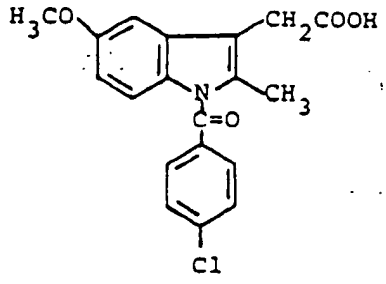
tolmetin



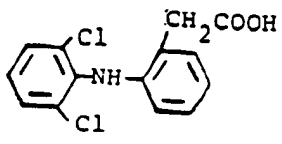
sulindac

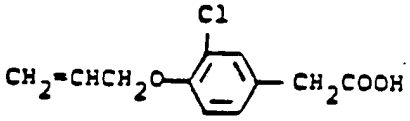


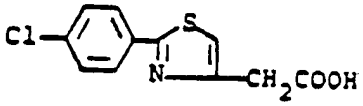
indomethacin

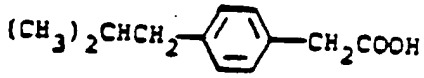


diclofenac



alclofenac 

fenclozic acid 

ibufenac 

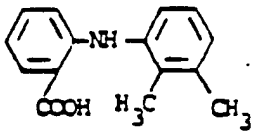
Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH_2COOH$ group, (which

optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH_2COO^-Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

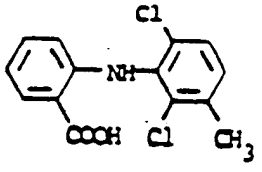
The fenamic acid derivatives for use herein include, but are not limited to, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Representative members of the fenamic acid group include mefenamic acid, meclofenamate sodium (meclofenamic acid, sodium salt) and flufenamic acid. Structural formulas for representative group members are set forth below:

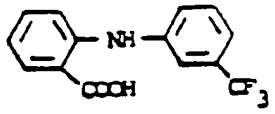
FENAMIC ACID DERIVATIVES

mefenamic acid

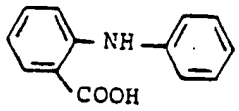


meclofenamic acid



flufenamic acid 

Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure

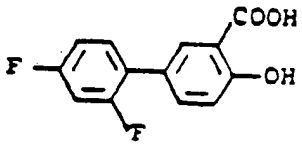


which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g. $-COO^{-}Na^{+}$.

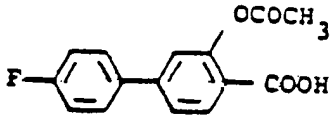
The biphenylcarboxylic acid derivatives for use herein include, but are not limited to, diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Representative members of this group are diflunisal and flufenisal, whose structural formulas are set forth below:

BIPHENYLCARBOXYLIC ACID DERIVATIVES

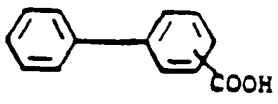
diflunisal



flufenisal



Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure

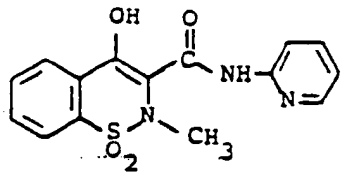


which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g. $-COO^{-}Na^{+}$.

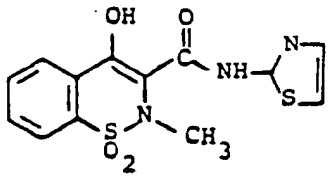
The oxicams for use herein include, but are not limited to, piroxicam, sudoxicam, isoxicam and CP-14,304. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Representative members of this group are depicted below:

OXICAMS

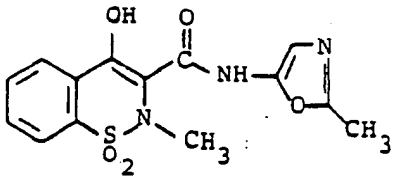
piroxicam



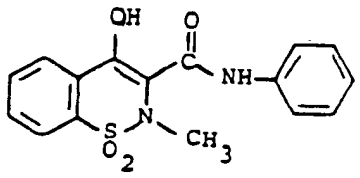
sudoxicam



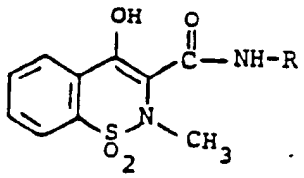
isoxicam



CP-14,304
[4-hydroxy-1,2-benzo-
thiazine 1,1-dioxide
4-(N-phenyl)-carboxamide]



Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula



wherein R is an aryl or heteroaryl ring system.

Of the propionic acid derivatives for use herein, ibuprofen, naproxen, naproxen sodium, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen, and fluprofen may be mentioned as particularly preferred compounds.

Of the acetic acid derivatives, presently preferred members include tolmetin sodium, sulindac and indomethacin.

Of the fenamic acid derivatives, particularly preferred compounds include mefenamic acid and meclofenamate sodium.

The particularly preferred biphenylcarboxylic acid derivatives for use in the pr sent invention include diflunisal and flufenisal.

The particularly advantageous oxicams include piroxicam, sudoxicam and isoxicam.

Of the foregoing non-st roidal anti-inflammatory drugs, in the practice of the preferred embodiments of the present invention, ibuprofen and naproxen are most preferred.

With respect to the dosage amount of the non-steroidal anti-inflammatory drugs in the formulations of the invention, although the specific dose will vary depending upon the age and weight of the patient, the severity of the symptoms, the incidence of side effects and the like, for humans, typical effective analgesic amounts of presently preferred NSAID's for use in unit dose compositions of the invention presented in milligrams are set forth in Table II; however, greater or lesser amounts may be employed if desired or necessary. A description of unit dose dispensing is presented in Remington's Pharmaceutical Sciences, Fifteenth Edition, pages 1698-9.

With respect to the compounds set forth hereinabove falling within the propionic acid derivative category, suitable dosage ranges for these compounds will generally fall within the range of about 12.5 mg to 900 mg in each unit dose. A general dosage range for those compounds that fall within the acetic acid derivative category is about 25 mg to 400 mg in each unit dose. A general dosage range for those compounds falling within the fenamic acid derivative category is about 50 mg to 500 mg in each unit dose. A general dosage range for those compounds falling within the biphenylcarboxylic acid derivative category is about 125 mg to 1000 mg in each unit dose. A general dosage range for those compounds falling within the oxicam category is about 10 mg to 40 mg in each unit dose.

TABLE II

DRUG	PREFERRED UNIT DOSE	MAX. TOTAL DAILY DOSE	WIDE RANGE UNIT DOSE
Diflunisal	125 - 500	1500	125 - 1000
Ibuprofen	100 - 400	2400	50 - 800
Naproxen	125 - 500	1250	125 - 750
Flurbiprofen	25 - 50	300	25 - 150
Fenoprofen	50 - 200	2400	50 - 300
Piroxicam	10 - 40	80	10 - 80
Mefenamic Acid	125 - 250	1250	125 - 500
Fenbufen	100 - 500	3000	100 - 900
Ketoprofen	25 - 150	1200	25 - 200
Naproxen Sodium	138 - 550	1375	138 - 825
Suprofen	100 - 400	1600	50 - 600

A complete description of the various NSAID's, including acceptable analgesically effective amounts thereof for use in unit dose compositions of the present invention also appears in applicants' U.S. Patent No. 4,486,436 and U.S. Patent No. 4,522,826.

The term "skeletal muscle relaxant" as used herein is intended to mean any compound having skeletal muscle relaxing properties. Any skeletal muscle relaxant is useful in the practice of the present invention. The skeletal muscle relaxants may be broadly classified as those that act directly on skeletal muscle and those that act on the level of the central nervous system. The centrally acting muscle relaxants block impulses at the interneurons of poly-synaptic reflex arcs, mainly at the level of the spinal cord. This is demonstrated by the abolishment of the diminution of the flexor and crossed extensor reflexes which possess one or more interneurons between the sensory and motor fibers. The knee-jerk response, which acts through a monosynaptic reflex system and therefore possesses no interneurons, is unaffected by this class of drugs.

These drugs also possess mild depressant properties on the CNS; the major sites of action are the brain stem and subcortical areas. The ascending reticular formation, which receives and transmits some sensory stimuli, transmits and maintains a state of arousal. When the passage of stimuli is blocked at the level of ascending reticular formation, response to sensory stimuli is reduced and depression ranging from sedation to anesthesia may occur. Suppression of poly-synaptic reflexes at the spinal cord level is not sufficient to account for depression of the arousal system.

Most of the clinically useful centrally acting skeletal muscle relaxants fall into the following chemical groups: glycerylmonoethers and derivatives, oxazoles, substituted alkanediols, benzazoles, benzodiazepines, 1,3-dioxalanes and miscellaneous. Since not all of the skeletal muscle relaxants readily lend themselves to such categorization, a miscellaneous category is required.

The skeletal muscle relaxant formulations of the present invention comprise, in addition to the non-steroidal anti-inflammatory drugs, at least one active ingredient from the above-described chemical groups. Typical examples of drugs contained within each chemical group are presented below:

a. glycerylmonoethers and derivatives
   - mephenesin
   - mephenesin carbamate
   - mephenesin acid succinate
   - methocarbamol
   - chlorphenesin carbamate

b. oxazoles
   - mephenoxalone
   - metaxalone

c. substituted alkanediols
   - meprobamate
   - carisoprodol

d. benzazoles
   - zoxazolamine
   - chlorzoxazone

e. benzodiazepines
   - chlordiazepoxide HCl
   - diazepam

f. miscellaneous
   - analexin

baclofen
chlormezanone
cyclobenzaprine HCl
orphenadrine citrate

Some centrally-acting muscle relaxants are presented in Table III along with their chemical structure, dosage forms and usual unit dose.

TABLE III

entrally-Acting Skeletal Muscle Relaxants

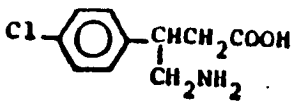
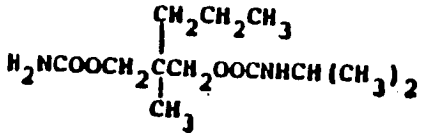
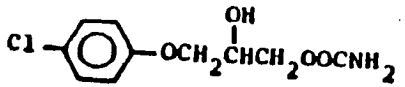
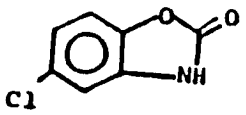
GENERIC NAME	CHEMICAL STRUCTURE	DOSAGE FORMS*	USUAL UNIT DOSE
Baclofen		T:10 mg	5-20 mg
Carisoprod l		T:350 mg	350 mg
Chlorphenesin arbamat		T:400 mg	800 mg
Chlorzoxazone		T:250 mg	250-750 mg

TABLE III (continued)

Centrally-Acting Skeletal Muscle Relaxants

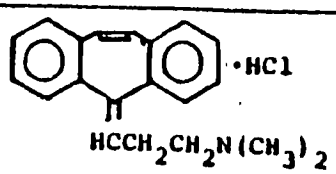
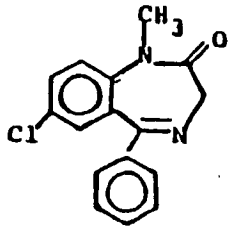
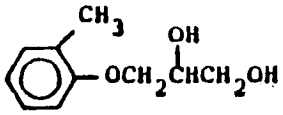
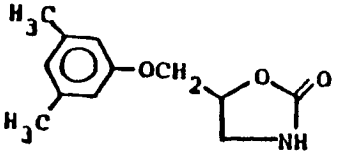
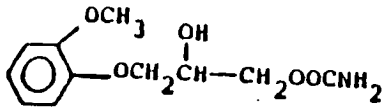
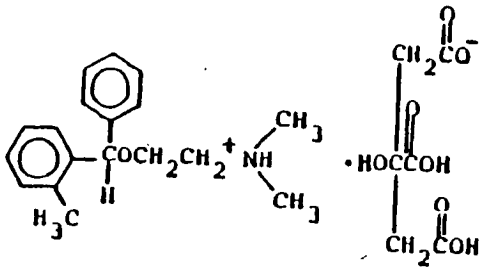
GENERIC NAME	CHEMICAL STRUCTURE	DOSAGE FORMS*	USUAL UNIT DOSE
Cyclobenzaprine Hydrochloride, U.S.P.		T:10 mg	10 mg
Diazepam		T:2,5,10 mg I:5 mg/ml	2-10 mg oral 2-15 mg i.m. or i.v.
Mephenesin		T:500 mg	1-2 g
Metaxalone		T:400 mg	800 mg

TABLE III (continued)

Centrally-Acting Skeletal Muscle Relaxants

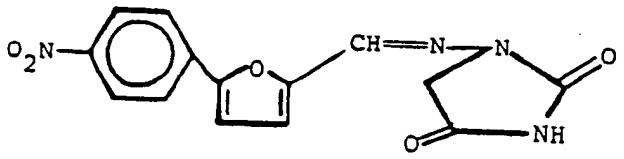
GENERIC NAME	CHEMICAL STRUCTURE	DOSAGE FORMS*	USUAL UNIT DOSE
Methocarbamol, U.S.P.		T:500,750 mg I:100 mg/ml	1-2 g. oral 1-3 g. i.v., slowly
Orphenadrine Citrate, U.S.P.		T:100 mg I:30 mg/ml	100 mg. oral 60 mg. i.m. or i.v.

*T=tablet; I=injection.

Mephensin has been the most extensively studied drug among the skeletal muscle relaxants. Although rarely used today it is a prototype for other skeletal muscle relaxants which have similar pharmacological actions. These include carisoprodol, chlorphenesin carbamate, chlorzoxazone, metaxalone, methocarbamol and orphenadrine citrate. Methocarbamol and orphenadrine citrate can be administered either orally or intraveneously. In the latter case, it is used to relieve severe, acute muscle spasm of local origin caused by inflammation or trauma. Other clinically useful skeletal muscle relaxants which differ from mephenesin in their pharmacological mode of action are the benzodiazepines (e.g., diazepam), baclofen and cyclobenzaprine. Diazepam and other benzodiazepines are used for a variety of spastic states but may be most useful in painful spasms of flexor muscles.

These drugs appear to have a more selective action on reticular neuronal mechanisms that control muscle tone than on spinal interneuronal activity, whereas mephensin-like drugs exhibit no such selectivity. Baclofen is used for the treatment of spasticity in patients with multiple sclerosis. Baclofen's usefulness is limited by its adverse effects which include drowsiness, insomnia, dizziness, etc. Cyclobenzaprine is closely related to the tricyclic antidepressants both structurally and pharmacologically and has side effects which are common with that group of drugs.

In addition to the centrally-acting muscle relaxants identified above, dantrolene is a typical non-centrally-acting muscle relaxant which exerts its effects by direct actions on skeletal muscle. Dantrolene has the following chemical structure:



Dantrolene reduces contraction of skeletal muscle by direct action on excitation-contraction coupling, perhaps by decreasing the amount of calcium released from the sarcoplamic reticulum. Although dantrolene produces some central nervous system depressant effects, it does not impair polysynaptic reflexes preferentially as do the centrally-acting muscle relaxants. Dantrolene sodium is available for oral use at 25 - 100 mg in a single dose or for intravenous administration up to a total of 10 mg/kg.

The preferred muscle relaxants intended for use in the practice of the present invention include diazepam, carisoprodol, chlorzoxazone, methocarbamol and orphenadrine citrate.

With respect to the dosage amount of the skeletal muscle relaxant in the formulations of the invention, although the specific dose will vary depending upon the age and weight of the patient, the severity of the symptoms, the incidence of side effects and the like, for humans, typical effective amounts of the presently preferred skeletal muscle relaxants for use in unit dose compositions of the invention are about 2 - 10 mg diazepam, 100 - 600 mg carisoprodol, 100 - 1000 mg chlorzoxazone, 200 mg - 1500 mg methocarbamol and 25 - 100 mg orphenadrine citrate.

For those compounds not indicated as memb rs of the preferred category their typical or suggested ranges of unit dose administration are well-known to

those in the art. The package insert of each product sets out the dosage ranges determined by the manufacturer. These dosage ranges are the general guidelines followed by those familiar with skeletal muscle relaxants.

The skeletal muscle relaxant may be centrally-acting or it may directly affect skeletal muscle tissue. The skeletal muscle relaxant may fall within one of the five structural categories indicated hereinabove.

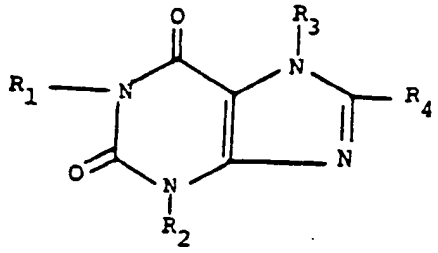
Several commercial centrally-acting skeletal muscle relaxants are currently available in the United States in formulations with aspirin or acetaminophen. The list of these currently available combination products is presented in Table I. These products are intended to provide an analgesic component to help relieve both the pain and in some cases the anxiety of the pain experience. Elenbass reviewed the published studies of such combination products in American Journal of Hospital Pharmacy, Vol. 37, Oct. 1980, pages 1313-1323. He concluded that the combination products provide ingredients to treat both the spasm and pain associated with musculoskeletal disorders, and they appear to provide better symptom relief than the individual agents. The AMA Drug Evaluations, 5th Ed., page 103 comment that results of some studies have alleged that a combination of muscle relaxant and an analgesic provides greater benefit in patients with acute musculoskeletal problems than similar doses of analgesic alone. The same page of AMA Drug Evaluations lists examples of combination skeletal muscle relaxants and analgesics.

Surprisingly, the present inventors now find that, the newer non-steroidal anti-inflammatory drugs, which differ substantially in chemical structure from aspirin, acetaminophen and phenacetin, and which have significantly different biological profiles therefrom can be advantageously formulated into a novel composition together with a skeletal muscle relaxant, and optionally xanthine or a xanthine derivative and administered to mammals, especially to humans, to obtain more pain relief and lessened adverse side effects.

Both Norgesic and Norgesic Forte contain caffeine. Many agents with muscle relaxant properties and which are in wide use in the treatment of muscle tension and pain associated with anxiety states and/or psychosomatic disorders produce notable sedation. An open question is whether the clinical benefits produced are the result of the sedative effect itself or whether they are actually eliciting muscle relaxant activity. A two-fold purpose could thus be achieved by adding a xanthine or a xanthine derivative such as caffeine to muscle relaxant formulations; the xanthine or xanthine derivative would enhance the activity of the non-steroidal anti-inflammatory agent while providing some degree of central nervous stimulation to compensate for the sedative effect of the skeletal muscle relaxant component itself.

In addition to the improved combination product heretofore described especially favorable results are obtained by further adding a xanthine or a xanthine derivative, in particular, caffeine, to the composition.

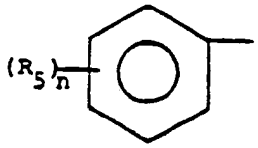
The xanthine derivatives of the invention comprise compounds of the general formula



or a pharmaceutically acceptable non-toxic salt thereof wherein

R_1-R_3, inclusive independently represent hydrogen, C_1-C_6alkyl (straight or branched), C_1-C_6alkoxy, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, hydroxy (C_1-C_6)alkyl, halogen, hydroxy(C_1-C_4)-alkylamino(C_1-C_4)alkyl, C_1-C_4(dialkyl)amino-(C_1-C_4)alkyl, C_1-C_4alkylcarbonyl(C_1-C_4)alkyl, C_1-C_6alkylamino, C_1-C_6(dialkyl)amino, indolyl, phenyl or allyl;

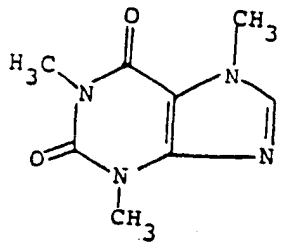
R_4 is hydrogen, C_1-C_6alkyl, halo(C_1-C_6)alkyl, C_1-C_6alkylamino, C_1-C_6alkylthio, nitro, carboxy, C_1-C_6(dialkyl)amino, C_3-C_6cycloalkyl, phenyl, naphthyl, ar(C_1-C_4)alkyl, or a group of the formula



where R_5 is halo, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, nitro, or C_1-C_6alkylamino and n is 1, 2 or 3.

A further discussion of xanthines and the xanthine derivatives is found in Applicants' copending application U.S. Patent No. 4,552,899.

Caffeine, or 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione, has the structural formula



The term "caffeine" as used herein is intended to encompass not only caffeine as the anhydrous powder, but any salt or derivative of caffeine or any compounded mixture thereof which is non-toxic, pharmaceutically acceptable and which is capable of enhancing an analgesic or anti-inflammatory response when employed as described herein. See, for example, The Merck Index, ninth edition, Merck & Co., Inc., Rahway, New Jersey (1976), pp. 207-208, for a description of caffeine salts, derivatives and mixtures which may prove useful in the compositions of the present invention. Nevertheless, caffeine as the anhydrous powder base is presently preferred and, where specific amounts of caffeine are set forth below, such amounts are given in mg of the anhydrous base.

When a selected NSAID and skeletal muscle relaxant are combined with a xanthine or xanthine derivative, such as caffeine, in accord with the present invention, the following unexpected results are produced:

(1) lower amounts of the selected NSAID are required for the same analgesic or anti-inflammatory effect;

(2) across all doses, a greater analgesic or anti-inflammatory response is achieved; and,

(3) some degree of central nervous system stimulation is provided to compensate for the possible sedative effect of the skeletal muscle relaxant.

Further, the ability of xanthine or a xanthine derivative, such as caffeine, to enhance analgesia or to enhance the anti-inflammatory response, i.e. to substantially reduce the amount of the selected NSAID which is required to elicit a given analgesic or anti-inflammatory response, is also a very important aspect of this invention. This finding permits the use of the selected NSAID in quantities substantially less than the dosages presently suggested as an analgesic or anti-inflammatory agent in humans. Use of lower doses should in turn lower the incidence and/or severity of undesirable side effects. Also, approximately one-fifth to one-third less of the NSAID can be used in the caffeine formulation to achieve the same analgesic or anti-inflammatory effect as that obtained by use of the selected NSAID alone; in other words, the addition of xanthine or a xanthine derivative, such as caffeine, decreases the amount of the selected non-steroidal anti-inflammatory agent used in the skeletal muscle relaxant formulation to about two-thirds to four-fifths of the usual amount to achieve the same effect. These ratios may vary, however, depending on the patient's individual response, the selected dosage level of the active ingredients, etc. Alternatively, at a given dosage level, a greater analgesic or anti-inflammatory response can be achieved.

The amount of xanthine or xanthine derivative in the analgesic composition will be an amount sufficient to enhance analgesia. For humans, in the case of caffeine, a unit dose composition will typically contain from about 60 to about 200 mg (preferably about 65 to about 150 mg) caffeine; this dosage level of caffeine is generally sufficient to enhance analgesia.

Certain NSAID's are particularly long-acting and need be administered less frequently than the usual every 4 to 6 hours; for example, diflunisal and naproxen are typically administered only twice daily and piroxicam only once a day. When such long-acting drugs are employed, it is often desirable to include an additional amount of a muscle relaxant and/or an additional analgesia-enhancing amount of caffeine in the composition in sustained release form.

Typical therapeutically active components of the present invention, along with their usual adult dosage, for use in the pharmaceutical compositions and methods of the present invention are set forth in the following Table IV. The third column indicates that caffeine is an optional third component in the compositions of the present invention. Among such Table IV, non-steroidal anti-inflammatory drugs in combination with caffeine, applicants have already demonstrated a surprisingly enhanced analgesic and anti-inflammatory response in a mammalian organism. Again, compare U.S. Patent Nos. 4,420,483, 4,464,376 and 4,479,956.

Illustrative of typical unit dose forms are tablets or capsules containing the amounts indicated in Table IV. Note that the asterisk (*) indicates that the adjacent amount is in sustained release form, e.g. "130 mg + 130 mg*" means that the first 130 mg is

formulated for immediate release, while the second 130 mg is in sustained release form.

TABLE IV

TYPICAL UNIT DOSES

Skeletal Muscle Relaxant	NSAID	OPTIONAL Caffeine
diazepam	ibuprofen	
2 mg	100 mg	65 or 130 mg
5 mg	200 mg	65 or 130 mg
10 mg	400 mg	65 or 130 mg
diazepam	naproxen	
2 mg + 2 mg*	125 mg	65 mg + 65 mg*
5 mg + 5 mg*	250 mg	130 mg + 130 mg*
10 mg + 10 mg*	500 mg	130 mg + 130 mg*
diazepam	fenoprofen	
2 mg	100 mg	65 mg or 130 mg
5 mg	200 mg	65 mg or 130 mg
10 mg	200 mg	65 mg or 130 mg
chlorzoxazone	ibuprofen	
250 mg	200 mg	65 or 130 mg
500 mg	400 mg	65 or 130 mg
chlorzoxazone	naproxen	
250 mg + 250 mg*	125 mg	65 mg + 65 mg*
500 mg + 500 mg*	250 mg	130 mg + 130 mg*
500 mg + 500 mg*	500 mg	130 mg + 130 mg*
chlorzoxazone	fenoprofen	
250 mg	100 mg	65 or 130 mg
500 mg	200 mg	65 or 130 mg
chlorzoxazone	piroxicam	
250 mg + 250 mg*	20 mg	65 mg + 65 mg*
250 mg + 250 mg*	20 mg	130 mg + 130 mg*
500 mg + 500 mg*	20 mg	130 mg + 130 mg*
carisoprodol	ibuprofen	
200 mg	200 mg	65 or 130 mg
400 mg	400 mg	65 or 130 mg

TABLE IV (continued)

Skeletal Muscle Relaxant	NSAID	OPTIONAL Caffeine
carisoprodol 200 mg + 200 mg* 200 mg + 200 mg* 400 mg + 400 mg*	naproxen 125 mg 250 mg 500 mg	 65 mg + 65 mg* 130 mg + 130 mg* 130 mg + 130 mg*
carisoprodol 200 mg + 200 mg* 200 mg + 200 mg* 400 mg + 400 mg*	diflunisal 250 mg 500 mg 500 mg	 65 mg + 65 mg* 130 mg + 130 mg* 130 mg + 130 mg*
methocarbamol 400 mg 800 mg	ibuprofen 200 mg 400 mg	 65 or 130 mg 65 or 130 mg
methocarbanol 400 mg + 400 mg* 400 mg + 400 mg* 800 mg + 800 mg*	naproxen 125 mg 250 mg 500 mg	 65 mg + 65 mg* 130 mg + 130 mg* 130 mg + 130 mg*
methocarbamol 400 mg + 400 mg* 800 mg + 800 mg*	sulindac 150 mg 200 mg	 65 mg + 65 mg* 130 mg + 130 mg*
orphenadrine citrate 25 mg 50 mg	ibuprofen 200 mg 400 mg	 65 or 130 mg 65 or 130 mg
orphenadrine citrate 25 mg + 25 mg* 25 mg + 25 mg* 50 mg + 50 mg*	naproxen 125 mg 250 mg 500 mg	 65 mg + 65 mg* 130 mg + 130 mg* 130 mg + 130 mg*
orphenadrine citrate 25 mg 50 mg	ketoprofen 25 mg 50 mg	 65 or 130 mg 65 or 130 mg

In accordance with the practices of the present invention, the NSAID/skeletal muscle relaxant compositions, containing xanthine or a xanthine derivative, may be administered in admixture with suitable pharmaceutical diluents, carriers or other excipients (collectively referred to as "carrier" materials) suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active drug components may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium-benzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc. Sweetening and flavoring agents and preservatives can also be included where appropriate.

Of course, additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components to optimize the therapeutic effects, i.e., analgesia, skeletal muscle relaxation, etc. while minimizing undesirable side

effects. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Similarly, injectable dosage units may be utilized to accomplish intravenous, intramuscular or subcutaneous administration and, for such parenteral administration, suitable sterile aqueous or non-aqueous solutions or suspensions, optionally containing appropriate solutes to effectuate isotonicity, will be employed.

The pharmaceutical compositions of the present invention may also be formulated and administered by other methods which are known for administering analgesics. The composition may be adapted for rectal administration, for example, as a suppository. The composition may also be adapted for topical application, for example, the composition may be applied in a pharmaceutically acceptable topical vehicle selected from the group consisting of creams, gels, ointments, powders, aerosols and solutions suitable for topical administration.

As representative suitable formulations consistent with the objects, features and advantages of the present invention, the following non-limiting examples are provided.

Example 1

Chlorzoxazone - 250 mg
Ibuprofen - 400 mg
Triturate active ingredients and q.s. with lactose to selected capsule size

Example 2

Methocarbamol - 400 mg
Fenoprofen - 200 mg
Triturate active ingredients and q.s. with lactose to selected capsule size

Example 3

Chlorzoxazone - 250 mg
Ibuprofen-400 mg
Caffeine - 130 mg
Triturate active ingredients and q.s. with lactose to selected capsule size

Example 4

Methocarbamol- 400 mg
Fenoprofen - 200 mg
Caffeine - 130 mg
Triturate active ingredients and q.s. with lactose to selected capsule size

From the foregoing, other typical acceptable pharmaceutical formulations will be apparent to those skilled in the art of pharmaceutical formulations.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. For example, effective dosages other than the preferred ranges set forth hereinabove with respect to the active ingredients may be applicable as a consequence of variations of the responsiveness of the mammal treated, severity of symptoms, dosage related adverse effects, if any, observed and similar considerations. Accordingly, such expected variations or differences in the practice of the present invention and the results obtained are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

CLAIMS:

1. A pharmaceutical composition of matter for use in the treatment of a skeletal muscle disorder in a mammal, said composition comprising:

(i) an effective amount of a skeletal muscle relaxant, and

(ii) an analgesically effective amount of a non-steroidal anti-inflammatory drug, wherein said non-steroidal anti-inflammatory drug comprises a propionic acid derivative, acetic acid derivative, fenamic acid derivative, biphenylcarboxylic acid derivative or an oxicam, or the pharmaceutically acceptable salts thereof.

2. A composition of matter as defined by Claim 1, wherein said propionic acid derivative comprises ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, ibuprofen aluminum, fenbufen, ketoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen or bucloxic acid.

3. A composition of matter as defined by Claim 1, wherein said acetic acid derivative comprises indomethacin, sulindac, tolmetin, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac or oxepinac.

4. A composition of matter as defined by Claim 1, wherein said fenamic acid derivative comprises

mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid or tolfenamic acid.

5. A composition of matter as defined by Claim 1, wherein said biphenylcarboxylic acid comprises diflunisal or flufenisal.

6. A composition of matter as defined by Claim 1, wherein said oxicam comprises piroxicam, sudoxicam or isoxicam.

7. A composition of matter as defined by Claim 1, wherein said skeletal muscle relaxant comprises a glycerylmonoether or a derivative thereof.

8. A composition of matter as defined by Claim 7, wherein said glycerylmonoether or a derivative thereof comprises mephenesin, mephenesin carbamate, mephenesin acid succinate, methocarbamol or chlorphenesin carbamate.

9. A composition of matter as defined by Claim 1, wherein said skeletal muscle relaxant comprises an oxazole.

10. A composition of matter as defined by Claim 9, wherein said oxazole comprises mephenoxalone or metaxalone.

11. A composition of matter as defined by Claim 1, wherein said skeletal muscle relaxant comprises a substituted alkanediol.

drug comprises about 100 mg to 400 mg ibuprofen and said skeletal muscle relaxant comprises about 2 mg to 10 mg diazepam.

20. A composition of matter as defined by Claim 1, wherein said non-steriodal anti-flammatory drug comprises about 100 mg to 400 mg ibuprofen and said skeletal muscle relaxant comprises about 100 mg to 600 mg carisoprodol.

21. A composition of matter as defined by Claim 1, wherein said non-steroidal anti-inflammatory drug comprises about 100 mg to 400 mg ibuprofen and said skeletal muscle relaxant comprises about 200 mg to 2000 mg methocarbamol.

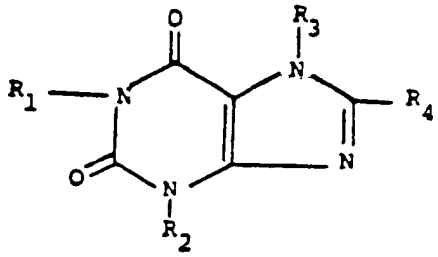
22. A composition of matter as defined by Claim 1, wherein said non-steroidal anti-inflammatory drug comprises about 100 mg to 400 mg ibuprofen and said skeletal muscle relaxant comprises about 25 mg to 100 mg orphenadrine citrate.

23. A composition of matter as defined by Claim 1, wherein said non-steroidal anti-inflammatory drug comprises about 125 mg to 500 mg naproxen and said skeletal muscle relaxant comprises about 100 mg to 1000 mg chlorzoxazone.

24. A composition of matter as defined by Claim 1, wherein said non-steroidal anti-inflammatory drug comprises about 125 mg to 500 mg naproxen and said skeletal muscle relaxant comprises about 2 mg to 10 mg diazepam.

(ii) an analgesically and anti-inflammatorily effective amount of a non-steroidal anti-inflammatory drug, wherein said non-steroidal anti-inflammatory drug comprises a propionic acid derivative, acetic acid derivative, fenamic acid derivative, biphenylcarboxylic acid derivative or an oxicam, or the pharmaceutically acceptable salts thereof, and

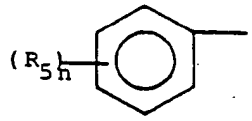
(iii) an amount of xanthine or xanthine derivative sufficient to enhance said analgesic and anti-inflammatory response, said xanthine derivative having the formula:



or a pharmaceutically acceptable non-toxic salt thereof wherein

R_1-R_3, inclusive, independently represent hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, hydroxy (C_1-C_6)alkyl, halogen, hydroxy (C_1-C_4)-alkylamino (C_1-C_4)alkyl, C_1-C_4(dialkyl) amino-(C_1-C_4)alkyl, C_1-C_4alkylcarbonyl (C_1-C_4)alkyl, C_1-C_6alkylamino, C_1-C_6 (dialkyl)amino, indolyl, phenyl or allyl;

R_4 is hydrogen, C_1-C_6alkyl, halo (C_1C_6)alkyl, C_1-C_6alkylamino, C_1-C_6alkylthio, nitro, carboxy, C_1-C_6(dialkyl)amino, C_3-C_6cycloalkyl, phenyl, naphthyl, ar(C_1-C_4)alkyl, or a group of the formula



where R_5 is halo, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, nitro or C_1-C_6alkylamino and n is 1, 2 or 3.

30. A composition of matter as defined by Claim 29, wherein component (iii) comprises a xanthine derivative wherein R_1 is C_1 alkyl, R_2 is C_1 alkyl, R_3 is C_1 alkyl and R_4 is hydrogen, said xanthine derivative being caffeine.

31. A composition of matter as defined by Claim 30, wherein said xanthine derivative comprises about 60 to about 200 mg caffeine.

32. A composition of matter as defined by Claim 29, wherein said propionic acid derivative comprises ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, ibuprofen aluminum, fenbufen, ketoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid.

33. A composition of matter as defined by Claim 29, wherein said acetic acid derivative comprises indomethacin, sulindac, tolmetin, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxepinac.

34. A composition of matter as defined by Claim 29, wherein said fenamic acid derivative comprises mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid.

35. A composition of matter as defined by Claim 29, wherein said biphenylcarboxylic acid comprises diflunisal and flufenisal.

36. A composition of matter as defined by Claim 29, wherein said oxicam comprises piroxicam, sudoxicam and isoxicam.

37. A composition of matter as defined by Claim 29, wherein said skeletal muscle relaxant comprises a glycerylmonoether or a derivative thereof.

38. A composition of matter as defined by Claim 37, wherein said glycerylmonoether or derivative thereof comprises mephenesin, mephenesin carbamate, mephenesin acid succinate, methocarbamol and chlorphenesin carbamate.

39. A composition of matter as defined by Claim 29, wherein said skeletal muscle relaxant comprises an oxazole.

40. A composition of matter as defined by Claim 39, wherein said oxazole comprises mephenoxalone and metaxalone.

41. A composition of matter as defined by Claim 29, wherein said skeletal muscle relaxant comprises a substituted alkanediol.

42. A composition of matter as defined by Claim 41, wherein said substituted alkanediol comprises meprobamate and carisoprodol.

43. A composition of matter as defined by Claim 29, wherein said skeletal muscle relaxant comprises a benzazole.

44. A composition of matter as defined by Claim 43, wherein said benzazole comprises zoxazolamine and chlorzoxazone.

45. A composition of matter as defined by Claim 29, wherein said skeletal muscle relaxant comprises a benzodiazepine.

46. A composition of matter as defined by Claim 45, wherein said benzodiazepine comprises chlordiazepoxide and diazepam.

47. A composition of matter as defined by Claim 29, wherein said skeletal muscle relaxant comprises analexin, baclofen, chlormezanone, cyclobenzaprine HCl, orphenadrine citrate and dantrolene.

48. A composition of matter as defined by Claim 29, wherein said non-steroidal anti-inflammatory drug comprises about 100 mg to 400 mg ibuprofen, said skeletal muscle relaxant comprises about 100 mg to 1000

mg chlorzoxazone and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

49. A composition of matter as defined by Claim 29, wherein said non-steroidal anti-inflammatory drug comprises about 100 mg to 400 mg ibuprofen, said skeletal muscle relaxant comprises about 2 mg to 10 mg diazepam and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

50. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory drug comprises about 100 mg to 400 mg ibuprofen, said skeletal muscle relaxant comprises about 100 mg to 600 mg carisoprodol and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

51. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory drug comprises about 100 mg to 400 mg ibuprofen, said skeletal muscle relaxant comprises about 200 mg to 1500 mg methocarbamol and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

52. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory drug comprises about 100 mg to 400 mg ibuprofen, said skeletal muscle relaxant comprises about 25 mg to 100 mg orphenadine citrate and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

53. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory

drug comprises about 125 mg to 500 mg naproxen, said skeletal muscle relaxant comprises about 100 mg to 1000 mg chlorzoxazone and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

54. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory drug comprises about 125 mg to 500 mg naproxen, said skeletal muscle relaxant comprises about 2 mg to 10 mg diazepam and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

55. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory drug comprises about 125 mg to 500 mg naproxen, said skeletal muscle relaxant comprises about 100 mg to 600 mg carisoprodol and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

56. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory drug comprises about 125 mg to 500 mg naproxen, said skeletal muscle relaxant comprises about 200 mg to 1500 mg methocarbamol and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

57. A composition of matter as defined by Claim 29, wherein said non-steriodal anti-inflammatory drug comprises about 125 mg to 500 mg naproxen, said skeletal muscle relaxant comprises about 25 mg to 100 mg orphenadine citrate and said xanthine or xanthine derivative comprises about 60 mg to 200 mg caffeine.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/02335

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 45/06; A 61 K 31/55; A 61 K 31/42; A 61 K 31/27

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with Indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Chemical Abstracts, volume 103, no. 2, 15 July 1985, Columbus, Ohio, (US) see page 340, abstract no. 11493j & RO, A, 82717 (MARINESCU, Ioan) 30 October 1983 --	1-27,29-57
A	US, A, 4486436 (A. SUNSHINE) 4 December 1984, see claims (cited in the application) --	1-27,29-57
A,P	US, A, 4522826 (A. SUNSHINE) 11 June 1985, see claims (cited in the application)	1-27,29-57

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[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st March 1986	23 AVR. 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	H. VAN MOL

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers °°)... because they relate to subject matter not required to be searched by this Authority, namely:

°°) 28,58 See PCT Rule 39.1(iv) Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods

2. [ ] Claim numbers....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 85/02335 (SA 11597)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 14/04/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4486436	04/12/84	BE-A-	897356	14/11/83
		FR-A-	2530469	27/01/84
		WO-A-	8400488	16/02/84
		WO-A-	8400490	16/02/84
		AU-A-	1881683	23/02/84
		AU-A-	1887783	23/02/84
		SE-A-	8401538	20/03/84
		EP-A-	0114886	08/08/84
		US-A-	4464376	07/08/84
		GB-A-	2134786	22/08/84
		DE-T-	3390116	10/01/85
		NL-T-	8320240	01/06/84
		US-A-	4567183	28/01/86
US-A- 4522826	11/06/85	BE-A-	901667	29/05/85
		WO-A-	8503443	15/08/85
		FR-A-	2559061	09/08/85
		SE-A-	8504612	04/10/85
		AU-A-	3935685	27/08/85
		GB-A-	2162747	12/02/86
		NL-A-	8520027	02/01/86